Pharmacology of Commonly Used Sedative Agents

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KEYWORDS

• Sedation • ICU • Pharmacology • Propofol • Benzodiazepine • Ketamine
• Barbiturate

KEY POINTS

- Propofol has ideal sedation-anesthetic properties but causes respiratory depression and hypotension. Prolonged infusions of propofol are associated with propofol-related infusion syndrome.
- Midazolam and lorazepam have long half-lives and increased risks of delirium and dependency or drug withdrawal.
- Ketamine offers unique analgesic and dissociative properties. It is associated with an emergence reaction and requires careful monitoring for cardiovascular effects.
- Barbiturates are reserved for refractory cases due to their narrow therapeutic index and risk of severe respiratory depression and bradyarrhythmias.

INTRODUCTION

This article aims to provide a contemporary evidence-informed review of the pharmacology of 4 sedatives commonly used in intensive care units (ICUs) worldwide. Specifically, this study focuses on propofol, benzodiazepines (midazolam and lorazepam), ketamine, and barbiturates (pentobarbital and phenobarbital) when administered by continuous intravenous (IV) infusion. Procedural indications will not be included.

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Abbreviations	
$GABA_A$	gamma-aminobutyric acid
ICP	intracranial pressure
ICUs	intensive care units
IV	Intravenous
LogP oct/wat	partition coefficient
NMDA	N-methyl-D-aspartate
PRIS	propofol-related infusion syndrome
Vd	volume of distribution

Other articles cover analgosedation, antipsychotics, alpha-2 agonists, and inhaled anesthetics. We will discuss mechanisms of action, physicochemical properties, pharmacokinetic-pharmacodynamic parameters (Table 1), and adverse effects that limit clinical use.

PROPOFOL

Mechanism of Action

Propofol (2,6-diisopropylphenol) is an agonist at the beta subunit of the gamma-aminobutyric acid ($GABA_A$) receptor, thereby reducing neuronal excitability.[1] Propofol also depresses excitatory neurotransmission through N-methyl-D-aspartate (NMDA) receptor antagonism.[1]

Formulation and Composition

Propofol is an oil-in-water emulsion consisting of egg lecithin, soybean oil, and glycerol, as it has poor water solubility. Case reports have garnered a manufacturer-issued contraindication in patients allergic to eggs or soy. However, large studies of food allergies have not demonstrated such cross-reaction with propofol.[2] The 1% emulsion has a caloric value of 1.1 kcal/mL, which should be considered when assessing nutrition in patients being administered continuous propofol.

Table 1
Definitions of common pharmacokinetic parameters

PK Parameters	Definition
Bioavailability (F)	Proportion of administered drug that reaches systemic circulation. For IV agents, F = 1
Volume of distribution (Vd)	Theoretic value describing the extent to which a drug distributes into body tissues relative to the plasma. Lower Vd (<0.4 L/kg) are predominant in the serum, whereas higher Vd (>0.7 L/kg) are highly tissue bound
Elimination half-life ($T_{1/2}$)	Time required for plasma concentration of a drug to decrease by 50%
Extraction ratio	Fraction of a drug removed during its passage through an organ of elimination, particularly the liver. These are classified as high (>0.7), intermediate (0.3–0.7), and low (<0.3)
Clearance	Volume of plasma from which a drug is completely removed per unit of time
Partition coefficient (LogP oct/wat)	Drug's distribution between lipophilic/octanol and hydrophilic/water environments

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Pharmacokinetics

Absorption and distribution

Propofol is highly lipophilic (LogP oct/water 4.3) allowing for rapid onset (30–60 seconds). This hydrophobic nature causes it to be highly protein bound—48% plasma protein binding (mostly albumin) and 50% erythrocytes.[3] The distribution kinetics of propofol adhere to a 3 compartment model where its high lipophilicity leads to rapid redistribution from serum into peripheral tissues (V_d 2–10 L/kg) and a short duration of action unless administered by continuous IV infusion.[1,4] Prolonged IV infusions may result in accumulation (V_d 60 L/kg) and longer duration of effect; this is referred to as context-sensitive $T_{1/2}$.[1,5] Decreased V_d in older adults might explain how sedation is achieved at lower doses.[6]

Metabolism and excretion

Propofol experiences extensive hepatic glucuronidation through 5'-diphosphate glucuronosyltransferase and hydroxylation through cytochrome P450 enzymes (CYP2B6 and CYP2C9) to inactive and water-soluble metabolites that are renally excreted.[7] Its high hepatic extraction ratio infers dependence on hepatic blood flow for its metabolism. Since propofol's serum clearance (1.6–3.4 L/min) exceeds overall hepatic perfusion, extrahepatic metabolism via kidneys and intestines also contributes significantly.[8] Hypothermia and genetic polymorphisms of CYP2B6 and GABA receptors also increase variability in drug metabolism.[7] Increased metabolic clearance may explain why women awaken from surgical anesthesia with propofol faster than men.[9]

Greater than 88% of its metabolites and less than 1% of the parent drug appear in the urine, and approximately 2% are excreted in the feces. Phenolic derivatives of propofol may impart an innocuous green coloring to urine.

Adverse Effects

Cardiorespiratory

Propofol exhibits dose-related negative inotropic effects, depressing cardiac contractility and output, and a decrease in systemic vascular resistance resulting in hypotension and sometimes bradycardia. Proposed mechanisms include negative chronotropic effects via action at the sinoatrial node, increased NO production, and sympathetic inhibition.[10,11]

Propofol is a potent respiratory depressant, and apnea may follow IV bolus dose administration. Studies have shown propofol reduces central CO_2 sensitivity in healthy volunteers and hyperpolarizes preinspiratory and expiratory neurons in the ventrolateral medulla in rats.[12,13]

Pancreatitis and hypertriglyceridemia

Prolonged propofol infusion is associated with hypertriglyceridemia and, less frequently, pancreatitis. Serum lipids should be obtained every 3 to 7 days for patients receiving an infusion greater than 48 hours or doses greater than 50 mcg/kg/min.[14] Propofol-associated pancreatitis is rare; in a large observational study of 7037 ventilated ICU patients, 20.8% had triglycerides greater than 400 mg/dL, and only 0.6% developed pancreatitis, of which 4 cases were deemed to be associated with propofol.[15] Serum triglycerides greater than 500 mg/dL is a reasonable threshold to consider reducing or discontinuing propofol.

Propofol-related infusion syndrome

Propofol disrupts electron transfer between mitochondrial complexes I and IV in a dose-dependent manner. Mitochondrial dysfunction results in heat irregularities and cellular hypoxia leading to cardiac failure and metabolic acidosis. Propofol may also interfere with fatty

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Table 2
Summary of retrospective studies, propofol-related infusion syndrome definitions, and outcomes[16–18]

Study	N	PRIS Definition Used	Incidence (%)	Mortality (%)	Propofol Infusion	Median Days to PRIS
Roberts et al,[16] 2009	1017	Metabolic acidosis plus cardiac dysfunction and ≥1 of rhabdomyolysis, hypertriglyceridemia, or renal failure after propofol initiation	1.1	18	Median: 5 d with 18% having >83 mcg/kg/min	3 d
Schroeppel et al,[17] 2014	207	Any 2 out of 4 of the following criteria: (1) cardiac arrhythmia or collapse, (2) metabolic acidosis, (3) rhabdomyolysis, and (4) acute kidney injury Must be after propofol initiation with no other known etiology	2.9	50	Median: 17.2 d at avg 36.7 mcg/kg/min	N/A
Li et al,[18] 2022	654	Definition 1: cardiac dysfunction and metabolic acidosis (major) + ≥2 minor criteria Definition 2: ≤1 major criteria + ≥3 minor criteria Minor criteria: rhabdomyolysis, hypertriglyceridemia, acute kidney injury, and hepatic transaminitis (rhabdomyolysis OR hypertriglyceridemia were required minor criteria)	2.9	36.8	Median: 6.125 d at 36.5 mcg/kg/min	5.2 d

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acid oxidation, which, along with its lipid emulsion, can result in hypertriglyceridemia, hepatomegaly, rhabdomyolysis, and electrocardiogram changes due to proarrhythmogenic fatty acids. The incidence and mortality of propofol-related infusion syndrome (PRIS) range from 1.1% to 2.9% and 18% to 50%, respectively, depending on the study definitions used (**Table 2**).[16–18] PRIS is a dose-dependent and duration-dependent phenomenon, with risk increasing after greater than 6 days at 35 mcg/kg/min or doses greater than 60 mcg/kg/min over 24 hours. Younger age, critical illness, traumatic brain injury, corticosteroids, and vasopressors are considered risk factors for PRIS given higher cumulative doses.[19] While hypertriglyceridemia can occur with PRIS, it does not share a causal relationship. One study found a reduction in the incidence of PRIS from 2.9% (6 out of 207) to 0.19% (2 out of 1038) when adopting a protocol of stopping propofol infusions for unexplained creatinine phosphokinase 5000 U/L or greater.[17]

BENZODIAZEPINES—MIDAZOLAM AND LORAZEPAM

Mechanism of Action

Benzodiazepines are allosteric modulators of the $GABA_A$ receptor.[20] They bind to alpha and gamma subunits of the receptor and potentiate the binding of endogenous GABA at a separate site.[20] This results in chloride ion influx, hyperpolarization, and resultant neuronal inhibition.[20] Their actions may be reversed with flumazenil, a short-acting, competitive $GABA_A$ antagonist.[21] Flumazenil is not routinely used for sedation reversal in ICU due to its association with agitation, supraventricular arrhythmias, and seizures.[21] This article focuses on midazolam and lorazepam, the most used benzodiazepines for critically ill patients.[22]

Formulation and Composition

Midazolam contains a methylated imidazole ring with pH-dependent solubility and a resultant shorter $T_{1/2}$ than other benzodiazepines.[23] At pH less than 4, the diazepine ring opens at the 5,6 position, resulting in a water-soluble amine derivative.[23] At physiologic pH, the equilibrium favors a closed structure, resulting in increased lipophilicity and V_d.[23] Both midazolam and lorazepam have small molecular weights and exhibit similar albumin binding (lorazepam ~85% bound; midazolam ~96% bound).[24] Without hypoalbuminemia, the primary differentiation in blood–brain barrier permeability is their lipophilicity. Midazolam is more lipophilic (LogP oct/water 4.33) than lorazepam (LogP oct/water up to 3.75), allowing a faster onset and shorter equilibration $T_{1/2}$ between brain and plasma concentrations.[24–26] This corresponds to shorter duration of action for intermittent bolus dosing.[24] Midazolam's extensive distribution into adipose has implications for patients with obesity or cachexia, wherein its V_d is increased and decreased, respectively.[27] Lorazepam is insoluble in water, and parenteral preparations use propylene glycol as a solvent.

Pharmacokinetics

Absorption and distribution

Midazolam and lorazepam pharmacokinetics are best described using a 2 compartment model.[28] Midazolam has an intermediate hepatic extraction ratio of 0.3 to 0.5, whereas lorazepam has a low hepatic extraction of 0.06.[29] Midazolam's reliance on hepatic blood flow for excretion may result in prolonged sedation in patients with cirrhosis, whereas lorazepam is minimally sensitive to changes in liver blood flow.[29,30]

Metabolism and excretion

Midazolam is metabolized primarily by hepatic CYP3A isozymes to active but less potent metabolites: alpha-hydroxy midazolam, 4-hydroxy midazolam, and alpha,4-dihydroxy

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midazolam.[29] Midazolam is subject to drug interactions with inducers and inhibitors of CYP3A. Patient factors such as age, sex, and inflammation have also been shown to affect CYP3A4 activity.[31] For example, pharmacokinetic studies have shown that women have 28% greater clearance of midazolam than men.[32] Common polymorphisms in CYP3A isozymes have not been consistently shown to alter midazolam clearance.[33] The most prevalent metabolite, alpha-hydroxy midazolam is 60% as potent as the parent compound, has a $T_{1/2}$ of approximately 0.8 to 1 hour, and is glucuronidated to an active metabolite that has 10% potency compared to midazolam.[20,34] This metabolite has an elimination $T_{1/2}$ approximately 1 hour and is excreted in the urine.[35] This may accumulate with renal dysfunction, though the clinical relevance is unknown due to its reduced potency. Like propofol, midazolam has a context-sensitive $T_{1/2}$.[36] Following discontinuation of a prolonged infusion, the time to return to baseline mental status may be prolonged.[36] Lorazepam undergoes glucuronidation to inactive metabolites.

Side Effects

Cardiorespiratory

Benzodiazepines may cause respiratory depression. Risk factors include high doses (such as midazolam >0.15 mg/kg in one study), concurrent opioid and/or propofol use, and renal dysfunction.[37,38] Dose-dependent hypotension may also occur, with prevalence ranging from 2.6% to 56% at doses up to 0.2 mg/kg/h midazolam and 10 mg/h lorazepam.[39,40] Possible mechanisms include vasodilation, decreased sympathetic tone, and reduced environmental stimulation due to sedation.[38] Benzodiazepines can also cause bradycardia due to negative inotropic effects, though incidence is less than with propofol and dexmedetomidine.[38–40]

Iatrogenic withdrawal

Abrupt cessation of benzodiazepines may result in a withdrawal syndrome that includes tachycardia, agitation, delirium, hallucinations, and seizures.[41] Iatrogenic withdrawal syndrome is associated with prolonged duration of mechanical ventilation and ICU length of stay.[41] The risk for withdrawal increases with prolonged use (>3–5 days) and high doses (>0.3 mg/kg/h or >60 mg/kg cumulative dose of midazolam in pediatric studies).[41] Mitigating factors include tapering regimens and the use of alpha-2 agonists.[42]

Delirium

Benzodiazepines have been strongly associated with delirium compared with other sedatives.[38] Given the association of delirium with prolonged duration of mechanical ventilation, increased hospital length of stay, and increased mortality, efforts to minimize the use of deliriogenic medications is prudent.[41] Accordingly, the Society of Critical Care Medicine 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption recommend propofol and dexmedetomidine over benzodiazepines.[43]

Propylene glycol toxicity

Lorazepam is solubilized with up to 80% v/v propylene glycol, an osmotically active solvent, that is, physically similar to ethylene glycol, though less toxic.[44] It is metabolized by hepatic alcohol dehydrogenase with lactate as a byproduct and is otherwise excreted unchanged in urine.[45] Toxicity is defined as a serum level greater than 25 mg/dL and may present as hyperosmolality, lactic acidosis, intravascular hemolysis, acute tubular necrosis, reduced level of consciousness, and seizures.[44,45] Risk factors for propylene glycol toxicity include liver or kidney dysfunction, prolonged infusions (>5 days), and higher doses (>1 mg/kg/h).[44,45]

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KETAMINE

Mechanism of Action

Ketamine is a nonselective, noncompetitive antagonist of the NMDA receptor at the phencyclidine binding sites.[46] Ketamine is a racemic mixture with S(+) ketamine having 3 times higher receptor affinity and anesthetic properties than R(−) ketamine. It also facilitates the release of endogenous catecholamines, which are agonists to mu, sigma, acetylcholine, and possibly GABA receptors. It may also inhibit voltage-gated sodium and potassium channels, and serotonin and dopamine transporters.[47] Ketamine induces a dissociative anesthetic state characterized by profound analgesia, amnesia, and a trance-like cataleptic state due to functional dissociation between thalamic, cortical, and limbic systems.[48]

Pharmacokinetics

Absorption and distribution

When administered IV, ketamine's onset of anesthetic action is less than 60 seconds. It is then rapidly distributed throughout the body. High lipophilicity (LogP octanol/water coefficient of 2.8) allows rapid transport through the blood–brain barrier. Its high V_d (2.1–3.1 L/kg) and relatively low protein binding of 27% determines its high intake by many tissues.[46] While a 2 compartment model has been used to describe the kinetic distribution of ketamine, more recent models that account for its many active metabolites describe a 7 compartment model.[49] Studies have shown a plasma concentration of 9.3 μM/L to achieve anesthetic effects, with recovery occurring at around 2.7 μM/L.[50]

Metabolism and excretion

Ketamine undergoes extensive hepatic metabolism including those of active metabolites. The racemic mixture initially undergoes N-dealkylation via CYP2B6 or CYP3A4 to norketamine, which further undergoes hydroxylation, conjugation, and dehydration, resulting in 4 predominant metabolites.[46] NMDA receptor potency varied from one-sixth to one-ninth of their respective parent enantiomer.[51] While there are no recommended dose adjustments in hepatic dysfunction, patients with impaired hepatic metabolism may respond to lower doses. Both parent drug and most active metabolites have high extraction ratios, emphasizing the role of hepatic function in preventing accumulation of ketamine and its metabolites.[52]

Over 90% of ketamine and its metabolites are renally eliminated with a high renal clearance of 12 to 17 mL/min/kg and minor fecal elimination. This results in an elimination $T_{1/2}$ of approximately 2.5 hours.[46,53]

Side Effects

As ketamine is used for both analgesia and sedation, it is important to distinguish their dosing parameters. The American Academy of Pain Medicine and the American Society of Anesthesiologists recommend boluses of less than 0.35 mg/kg and adding that infusions below 0.5 mg/kg/h likely suffice for acute pain.[54] While this is no clinically agreed upon threshold for an anesthetic infusion dose, most manufacturers recommend doses starting at 1 mg/kg/h. Infusion dosing in between 0.5 and 1 mg/kg/h are considered higher risk for ketamine emergence reactions. Given its multiple mechanisms of action, the use of ketamine in a variety of ICU settings has been shown to decrease opioid needs and potentially reduce vasopressor and sedation requirements.[55,56] It is still important to recognize the side effect profile of ketamine, how they occur, and prevention options (**Table 3**).

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Table 3
Summary of ketamine adverse effects, proposed mechanisms, and clinical considerations[57–62]

Problem	Proposed Mechanism	Clinical Considerations
Emergence phenomenon (delirium and hallucinations)	Prolonged depression of auditory and visual relay nuclei, leading to misperception, and/or misinterpretation of audio–visual stimuli Possible regions include the hippocampus and medial prefrontal[57]	• Dose-related effect with highest susceptibility between 0.5 and 1 mg/kg/h • Judicious titration is warranted • Can be pretreated or treated with benzodiazepines or concurrent propofol[58]
Transient apnea/laryngospasm	Rapid boluses may result in limited apnea/laryngospasms, usually when attempting intubations as ketamine does not suppress pharyngeal and laryngeal reflexes	• Contrary to bronchodilation from its sympathomimetic effects • Overcome with lower doses and slower pushes for induction
Airway secretions	Cholinergic receptor agonist, resulting in increased salivary and bronchial secretion	• Anticholinergic agents like atropine have been used to combat this effect[59]
Hypertension and tachycardia	Direct sympathomimetic effects	• Ketamine has some direct negative inotropic effects as well • Studies on induction show patients with a shock index $\geq$0.9 generally experience hypotension, whereas those with a shock index of <0.9 experienced greater incidences of tachycardia and hypertension[60] • "Significant" hypertension is a package label contraindication • Increase in ICP has been a historical concern, but recent evidence suggests this risk is minimal and perhaps negligible[61]
Toxicity/Overdose	Exaggerated presentation of the above symptoms, including hypertensive crisis, arrhythmias, psychosis, nystagmus, seizures, hypertonia, and dystonia	• Treated with supportive care, benzodiazepines for psychosis and seizures, and diphenhydramine for dystonia • There are no established thresholds for ketamine toxicity • Overdoses are primarily polysubstance, with almost no reports of mortality in therapeutic settings[62]

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BARBITURATES

Mechanism of Action

Barbiturates like pentobarbital and phenobarbital are substituted derivatives of barbituric acid that act as allosteric modulators of the $GABA_A$ receptor, similarly to benzodiazepines.[63] Barbiturates bind to $GABA_A$ receptors at distinct sites from benzodiazepines and the endogenous ligand GABA.[63] Their action prolongs channel opening, resulting in sustained chloride influx and inhibitory activity. Barbiturates are also antagonists at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, which reduces glutamatergic excitation.[63] At higher concentrations, barbiturates also inhibit rapid-firing voltage-gated sodium channels.[64] Administration of barbiturates for sedation can produce a range from light sedation to deep coma.[63] Due to their adverse effects and narrow therapeutic ranges, barbiturates are typically reserved for status epilepticus or elevated intracranial pressure (ICP) that is refractory to standard therapy.[65]

Physicochemical Properties and Formulations

Pentobarbital is the primary active metabolite of the formerly used thiopental. Phenobarbital is a phenylated barbital derivative.[63,66] Phenobarbital is also one of the metabolites of primidone.[66] Both pentobarbital and phenobarbital can be administered by IV infusion. They are also both lipophilic and their parenteral formulations contain PG as a solvent, up to 70% v/v.[67]

Pharmacokinetics

Absorption and distribution

Barbiturate pharmacokinetics are most commonly described by 1 compartment models.[65,68] Phenobarbital has low intrinsic hepatic clearance, which also renders it insensitive to changes in hepatic blood flow.[69] Both barbiturates are highly lipophilic and distribute readily into liver, brain, and kidney tissue.[69] Given its increased lipophilicity (LogP oct/water 2.1 compared to 1.47 for phenobarbital) pentobarbital more rapidly penetrates the blood–brain barrier and readily redistributes into peripheral tissues, with a resultant shorter duration of action, ranging from 3 to 4 hours.[70,71] This often results in its administration as a continuous infusion. With prolonged infusions, pentobarbital accumulates in adipose tissue.[72] Barbiturates exhibit moderate albumin binding; pentobarbital is 35% to 70% bound and phenobarbital is 50% bound.[68,72] Phenobarbital is a weak acid, such that in acidemia, the V_d increases as the drug more readily crosses the blood–brain barrier.[65]

Metabolism and excretion

Phenobarbital is metabolized primarily by CYP2C9 to inactive metabolites, with minor contributions from CYP2C19, CYP2E1, and glucuronidation.[63] Poor metabolizers of CYP2C19 may exhibit slower clearance of phenobarbital.[73] CYP2C9*2 carriers have shown increased likelihood to develop severe cutaneous adverse reactions.[74] Phenobarbital's inactive metabolites are eliminated in the urine, with less than 1% of the parent compound eliminated unchanged.[63] It induces CYP2A, 2B, and 2C isozymes, and thus, it may induce its own metabolism.[75] Pentobarbital also undergoes hepatic hydroxylation, though specific enzymes involved are not clear.[76] Given their structural similarities, it is assumed that phenobarbital and pentobarbital are both substrates and inducers of similar CYP enzymes.[75] Screening for drug interactions should take place for all patients receiving barbiturates. Population pharmacokinetics of phenobarbital are variable, with an apparent dose-dependent and duration-dependent $T_{1/2}$ up to 140 hours.[77]

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Therapeutic Drug Monitoring

Therapeutic drug monitoring may be useful for phenobarbital due to its narrow therapeutic index, variable clearance, and linear pharmacokinetics.[66] There are no high-quality data correlating efficacy or toxicity with phenobarbital serum concentrations, though the usual quoted therapeutic range is 10 to 40 mg/L for seizures (multiply by 4.31 for μmol/L), and may be extrapolated for use in other conditions.[66] Serum concentrations increase linearly with dose. Phenobarbital's long $T_{1/2}$ also means samples can be collected without regard to the time within the dosing interval, as fluctuations in concentrations are negligible.[66] Its long $T_{1/2}$ also means it may take several weeks of continuous use to achieve steady-state concentrations.[66] Such prolonged courses are not common and could be associated with delayed clearance following drug discontinuation.[72] Since phenobarbital is the active metabolite of primidone, phenobarbital drug level monitoring can be considered for patients on primidone.

Adverse Effects

Cardiorespiratory

Phenobarbital and pentobarbital may cause dose-dependent hypotension, respiratory depression, and bradyarrhythmias.[78] Possible mechanisms of cardiovascular toxicities include depression of medullary vasomotor centers, and polyethylene glycol (PG) toxicity.[72] Hypokalemia has been described during barbiturate coma therapy, with cases of refractory hyperkalemia following discontinuation.[79] Patients may develop tolerance to the sedative effects.[66] High doses may cause loss of brainstem reflexes and confound neurologic assessment.[66]

Gastrointestinal

Rarely, barbiturates have been associated with paralytic ileus that is unresponsive to prokinetic therapies.[80]

Propylene glycol toxicity

Like lorazepam, parenteral formulations of pentobarbital and phenobarbital contain propylene glycol, with concentrations ranging from 40% to 70% v/v.[67] Toxicity is most commonly defined as a serum propylene glycol concentration greater than 25 mg/dL, and it has been reported in patients requiring greater than 5 mg/kg/h of pentobarbital.[45,67] Patients should be monitored for signs and symptoms of propylene glycol toxicity, including hyperosmolarity, lactic acidosis, hemolysis, acute kidney injury, altered mental status, and seizures.[67] Serum osmolality may be used to screen patients at risk for toxicity.[45]

DISCLOSURE

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